

wherein the preformed lipid vesicles comprise a charged lipid which has a charge which is opposite to the charge of the charged therapeutic agent and a modified lipid having a steric barrier moiety for control of aggregation, and wherein the modified lipid is present in the preformed vesicles in an amount effective to retard, but not prevent, aggregation of the preformed vesicles.

14. The method of claim 13, wherein the charged lipid in the preformed lipid vesicles comprises a cationic lipid and the therapeutic agent is an anionic therapeutic agent.

15. The method of claim 14, wherein the cationic lipid is selected from the group consisting of

- dioleyl-N,N-dimethylammonium chloride ("DODAC");
- N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA");
- N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP");
- 3 β -(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol");
- N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE");
- cationic liposomes comprising DOTMA and 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE");
- cationic liposomes comprising N-(1-(2,3-dioleoyloxy)propyl)-N-(2-(sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoroacetate ("DOSPA") and DOPE;
- cationic lipids comprising dioctadecylamidoglycyl carboxyspermine ("DOGS") in ethanol;
- N-(2,3-dioleoyloxy)propyl)-N,N-dimethylammonium chloride ("DODMA") and
- 1,2-Dioleoyl-3-dimethylammonium-propane ("DODAP").

16. The method of claim 14, wherein the therapeutic agent is a polynucleotide.

17. The method of claim 16, wherein the cationic lipid is selected from the group consisting of

dioleyl-N,N-dimethylammonium chloride ("DODAC");
N-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA");
N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); -(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP");
3 β -(N-(N',N'-dimethylaminoethane)-carbonyl)cholesterol ("DC-Chol");
N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE");
cationic liposomes comprising DOTMA and 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE");
cationic liposomes comprising N-(1-(2,3-dioleyloxy)propyl)-N-(2-(sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoroacetate ("DOSPA") and DOPE;
cationic lipids comprising dioctadecylamidoglycyl carboxyspermine ("DOGS") in ethanol;
N-(2,3-dioleyloxy)propyl)-N,N-dimethylammonium chloride ("DODMA") and
1,2-Dioleoyl-3-dimethylammonium-propane ("DODAP").

18. The method of claim 16, wherein the lipid composition comprises 10 to 40 mol % of the charged lipid, 25 to 40 mol % of a neutral lipid; 35 to 55 mol % of a sterol, and 2.5 to 10 mol % of the modified lipid.

19. The method of claim 14, wherein the lipid composition comprises 10 to 40 mol % of the charged lipid, 25 to 40 mol % of a neutral lipid; 35 to 55 mol % of a sterol, and 2.5 to 10 mol % of the modified lipid.

20. The method of claim 13, wherein the lipid composition comprises 10 to 40 mol % of the charged lipid, 25 to 40 mol % of a neutral lipid; 35 to 55 mol % of a sterol, and 2.5 to 10 mol % of the modified lipid.

21. The method of claim 13, wherein the destabilizing agent is ethanol.
22. The method of claim 13, wherein the ethanol is present in the destabilizing solvent at a concentration of 25-40 %.
23. The method of claim 22, wherein the charged lipid comprises a cationic lipid selected from the group consisting of
dioleyl-N,N-dimethylammonium chloride ("DODAC");
N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA");
N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); -(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP");
3 β -(N-(N',N'-dimethylaminoethane)-carbonyl)cholesterol ("DC-Chol");
N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE");
cationic liposomes comprising DOTMA and 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE");
cationic liposomes comprising N-(1-(2,3-dioleoyloxy)propyl)-N-(2-(sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoroacetate ("DOSPA") and DOPE;
cationic lipids comprising dioctadecylamidoglycyl carboxyspermine ("DOGS") in ethanol;
N-(2,3-dioleoyloxy)propyl)-N,N-dimethylammonium chloride ("DODMA") and
1,2-Dioleoyl-3-dimethylammonium-propane ("DODAP").
24. The method of claim 22 wherein the destabilizing solvent further comprises 25 - 300 mM citrate buffer.
25. The method of claim 13, wherein the destabilizing agent is a detergent.

26. The method of claim 25, wherein the charged lipid comprises a cationic lipid selected from the group consisting of

dioleyl-N,N-dimethylammonium chloride ("DODAC");
N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA");
N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); -(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP");
3 β -(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol");
N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE");
cationic liposomes comprising DOTMA and 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE");
cationic liposomes comprising N-(1-(2,3-dioleoyloxy)propyl)-N-(2-(sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoroacetate ("DOSPA") and DOPE;
cationic lipids comprising dioctadecylamidoglycyl carboxyspermine ("DOGS") in ethanol;
N-(2,3-dioleoyloxy)propyl)-N,N-dimethylammonium chloride ("DODMA") and
1,2-Dioleoyl-3-dimethylammonium-propane ("DODAP").

27. The method of claim 25, wherein the destabilizing solvent further comprises 25 - 300 mM citrate buffer.

28. The method of claim 25, wherein the destabilizing solvent comprises 25 - 300 nM citrate buffer.

29. The method of claim 28, wherein the charged lipid comprises a cationic lipid selected from the group consisting of

dioleyl-N,N-dimethylammonium chloride ("DODAC");

N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTMA");
 N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); -(2,3-dioleoyloxy)propyl)-
 N,N,N-trimethylammonium chloride ("DOTAP");
 3 β -(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol");
 N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide
 ("DMRIE");
 cationic liposomes comprising DOTMA and 1,2-dioleoyl-sn-3-phosphoethanolamine
 ("DOPE");
 cationic liposomes comprising N-(1-(2,3-dioleoyloxy)propyl)-N-(2-
 (sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoroacetate ("DOSPA") and DOPE;
 cationic lipids comprising dioctadecylamidoglycyl carboxyspermine ("DOGS") in ethanol;
 N-(2,3-dioleoyloxy)propyl)-N,N-dimethylammonium chloride ("DODMA") and
 1,2-Dioleoyl-3-dimethylammonium-propane ("DODAP").

30. The method of claim 13, wherein the mixture is incubated at a temperature of about 40°C.

31. The method of claim 13, wherein the modified lipid is PEG-CerC₁₄.

32. The method of claim 13, wherein the preformed lipid vesicles comprise:
 a cationic lipid,
 a neutral lipid selected from the group consisting of DOPE and DSPC;
 the modified lipid, and
 cholesterol.